Charles Marc Samama

Aprotinin and major orthopedic surgery

Received: 22 April 2004
Accepted: 30 April 2004
Published online: 2 July 2004
© Springer-Verlag 2004

C. M. Samama (✉)
Département d'Anesthésie-Réanimation,
Hôpital Avicenne,
125, route de Stalingrad,
93009 Bobigny cedex, France
Tel.: +33-1-48955591,
Fax: +33-1-48955589,
e-mail: cmsamama@invivo.edu

Abstract Aprotinin is a potent pharmacological agent that reduces bleeding and limits blood transfusion requirements in current surgical practice. Many studies have been conducted in orthopedic surgery. In several trials performed in total hip replacement (THR) and total knee replacement (TKN) patients, aprotinin only moderately decreased blood-loss-replacement requirements. Conversely, when aprotinin was used in patients at high risk for bleeding (cancer, sepsis, redone surgery), it developed a potent hemostatic activity and decreased blood

transfusion significantly. No increase in deep vein thrombosis and pulmonary embolism was observed. The only major side effect could be the potential occurrence of an anaphylactoid reaction. Prophylactic administration of aprotinin should be considered in extensive spine surgery and in high-risk major orthopedic operations. The decision to use aprotinin should be guided by a risk/benefit analysis.

Keywords Aprotinin · Bleeding · Transfusion · Orthopaedic surgery · Thrombosis

Introduction

Aprotinin constitutes an interesting means to control or to reduce bleeding and to limit blood transfusion in current surgical practice. The interest in this antifibrinolytic drug dramatically increased when Royston et al. demonstrated, for the first time, the effect of high doses of aprotinin in reducing intraoperative blood loss and transfusions in cardiac surgery [26]. Since then, many studies have been performed in this type of setting. Aprotinin is widely used in cardiac surgery and trials have taken place in vascular [12] and liver transplant surgery [25], studying different dosages and modes of administration. Generally, aprotinin was able to decrease intraoperative and postoperative bleeding and blood transfusion. Many studies have also been conducted in orthopedic surgery [2, 3, 8, 13, 14, 15, 17, 19, 20, 22, 23, 28, 29, 30]. Some of the earliest trials were performed in total hip replacement (THR) and total knee replacement (TKN) patients. The general feeling was that aprotinin moderately decreased blood loss in these patients [8–14]. One or two packed red-cell units

per patient could be saved when this drug was used. Therefore, it was doubtful that such a compound could be used systematically in such settings. In contrast, the use of aprotinin in a double-blinded study [3] in high-risk septic and cancer patients undergoing pelvic and hip surgery proved to be effective in significantly reducing the need for blood transfusion, as compared with a placebo group. Even with a small number of patients, Capdevila et al. isolated for the first time an orthopedic setting in which aprotinin was very effective [3]. Only major orthopedic surgery with major bleeding events and increased risk of transfusion benefited from aprotinin in this study. Starting from this observation, we will review aprotinin's mechanism of action and the different studies in which it has been used; and we will try to define precisely a frame for the use of this potent hemostatic agent.

How does aprotinin work?

Aprotinin is a naturally occurring single-chain 58 amino-acid polypeptide with a molecular weight of 6,512 dalton.

It develops a broad inhibitory specificity on serine protease, but its most important effect is to inhibit plasmin, trypsin and kallikreins of various origins [27]. It forms a stoichiometric complex and blocks the active site of the enzyme. It is a competitive inhibition. Nevertheless, the mechanism underlying the beneficial effects of aprotinin in orthopedic surgery have not yet been fully elucidated. Several hypotheses can be proposed. Aprotinin acts mainly as an antiplasmin agent. However, no systemic fibrinolysis has ever been reported in scheduled orthopedic surgery [3, 8, 14]. For instance, coagulation and fibrinolytic parameters (thrombin-antithrombin (TAT) and plasmin-antiplasmin (PAP) complex, alpha2-antiplasmin, tissue plasminogen activator (t-PA), plasminogen activator inhibitor (PAI 1), D-dimers and factor XII were measured after a selective blood sampling in the femoral vein during total knee arthroplasty [8]. The only relevant result was an increase in the alpha2-antiplasmin level in the aprotinin group at 5 min and 240 min.

The occurrence of a local fibrinolysis has already been advocated, but never demonstrated. The anti-kallikrein activity of aprotinin interferes with the intrinsic coagulation pathway that is activated during severe sepsis. Therefore, aprotinin could prevent this activation, and, while decreasing thrombin generation, limit the extent of potential disseminated intravascular coagulation and platelet activation, both responsible for intraoperative bleeding.

Studies showing a lack of efficacy or a mild efficacy of aprotinin

Several trials first investigated the usefulness of aprotinin in hip or knee replacement patients [8, 14]. The results on blood loss and transfusion sparing were not so impressive and did not lead to any significant modification of the care of these patients. In 1994, Janssens was the first to compare, in a double-blinded fashion, giving either aprotinin as a bolus of 2 million kallikrein-inhibiting units (KIU) followed by an infusion of 0.5 million KIU/h until the end of surgery, or giving an equivalent volume of normal saline, in patients undergoing total hip replacement surgery [14]. Aprotinin reduced total blood loss from 1,943 ml to 1,446 ml. Total amounts of blood transfused were 3.4 units/patient in the control group and 1.8 units in the aprotinin group.

A study by Murkin was performed in patients undergoing revision or total hip arthroplasty [22]. The difference was statistically significant, but the amount of spared blood loss was not very large and the RBC transfusion decreased from 3 units in the control group to 2 units in the aprotinin group. Of note, the patients were also assessed for development of deep vein thrombosis (DVT) by lower-limb-compression ultrasound. None of the aprotinin patients and three placebo-treated patients demonstrated DVT.

In a second study from the same author, three aprotinin groups were compared with placebo in patients undergoing primary total hip replacement [23]. Aprotinin reduced total intraoperative blood loss and postoperative drainage volume, with a mean total of 1,408 ml for the placebo group compared with 1,079 ml in the "high-dose" group (i.e., 2 million KIU bolus + 0.5 million KIU/h), and a comparable moderate decrease was observed in the two other groups, with much smaller aprotinin doses. Furthermore, the percentage of patients who required any form of transfusion was small, 47% in the placebo group, leading to a reconsideration of the benefit of hemostatic drugs in such a setting.

A randomized, double-blinded controlled study by Langdown compared the effects of aprotinin (1.5 million KIU as a bolus, with no continuous infusion) with saline during primary total hip replacement in 60 patients [19]. No effect either on blood loss or transfusion was observed. Once again, as is often observed in negative studies, intraoperative and postoperative bleeding was small both in the placebo group (303 ml+525 ml) and in the aprotinin group (284 ml+550 ml).

Negative results were also found in 40 THR patients treated by aprotinin (2 million KIU) or placebo [13]. Total blood loss only reached 1,200 ml in both groups and transfusion requirements were unchanged.

Kasper reported negative results when comparing, retrospectively, two cohorts of patients (total $n=372$) who had undergone unilateral primary hip arthroplasty [16]. No difference was observed between the patients treated and not treated by aprotinin (almost 1.5 million KIU as a bolus before surgery). As expected, the blood loss in the control group was small (810 ml).

In total knee replacement (TKN) patients, the median blood loss of aprotinin patients (total dose 2 million KIU) was decreased to 663 ml as compared with 960 ml in the control group, and the median number of RBC units transfused was 0 in the aprotinin group as compared with 2 in the control group [29]. One patient with peripheral vascular disease developed an ischemia and underwent an amputation. This adverse event led to the study's interruption.

A second study was conducted more recently in 36 TKN patients [8]. No difference was observed between the aprotinin group (1 million KIU bolus followed by an infusion of 0.5 million KIU), the tranexamic acid group and the placebo. The mean blood loss (810 ml (245 ml–1,370 ml) was comparable in the three groups.

A study by Khoshhal including 43 patients over the age of 12 years demonstrated a moderate benefit of aprotinin (dose equivalent to the 2 million KIU+0.5 million KIU dose) vs placebo in spinal fusion for idiopathic scoliosis (10 levels of fusion in each group) [17]. The aprotinin group had less blood loss (831 ml vs 1,403 ml) and the transfusion requirement was less in the aprotinin group than the placebo group (–46%). However, the difference was

not significant statistically. It should be emphasized that the lack of efficacy could be related to the small amount of bleeding.

Finally, a randomized, double-blinded, placebo-controlled trial by Amar et al. included 69 adults with malignancy, scheduled for either pelvic, extremity or spine surgery during general anesthesia. It compared aprotinin ($n=23$, bolus of 2 million KIU, followed by an infusion 0.5 million KIU/h) with epsilon-amino caproic acid (EACA) ($n=22$, bolus of 150 mg/kg, followed by a 15 mg/kg/h infusion) and saline placebo ($n=24$) [2]. The study was negative; the groups did not differ in age, duration of surgery, perioperative blood loss or number of packed erythrocyte units transfused. However, this well-designed study could be criticized for several things: first, it was unfortunately underpowered, because it was terminated before full accrual of the projected sample size, based on the results of an early interim analysis; second, the population was very heterogeneous; and the third, and probably major, concern was that the amounts of blood loss and transfusion were very small in the control group – respectively 1.31 (0.6–1.9 l) and 1 packed red-cell unit (0–2 units) 48 h after surgery. This very small amount of bleeding could be related to active warming and/or controlled hypotension, or to very meticulous care of intraoperative hemostasis.

To summarize, major bias can be evidenced from all these studies. Obviously, hip or knee surgeries do not seem to be the most appropriate settings to use aprotinin. Bleeding is limited, and the usual perioperative amount of transfused RBC units generally does not exceed 3 units, which can be provided by a scheduled predonation. Surprisingly, these disappointing results can also be observed in spine and/or major orthopedic surgery, provided that the amount of perioperative bleeding is not large.

Prophylactic administration of aprotinin should be considered in extensive spine surgery and in high-risk major orthopedic operations

Several studies have investigated the benefit of aprotinin in spine surgery. A large prospective study by Lentschner in posterior lumbar spine fusion has shown interesting results in regard to the design of the surgical setting [20]. Seventy-two patients were randomized into two groups: the aprotinin group received the usual 2 million KIU dose as a bolus followed by a continuous infusion (0.5 million KIU/h). An additional bolus of 0.5 million KIU of aprotinin was infused every three RBC units. Each patient in the control group received equivalent volumes of saline solution. One to three spine levels were fused. The total blood loss was significant in the placebo group (2,760 ml (1,160 ml–5,000 ml) and reduced to 1,935 ml (600 ml–4,280 ml) by aprotinin. The total number of RBC units (either autologous or homologous) was not as high in the control group (2.5 units (0–6 units), but it was decreased

by aprotinin (0 units (0–5 units)). However, in this study, despite (or because of?) strong transfusion triggers, aprotinin therapy significantly decreased autologous, but not homologous, transfusion requirements in posterior lumbar spine fusion.

Sixty patients scheduled for elective, sequential antero-posterior thoracolumbosacral fusion were randomly assigned into three groups: control, epsilon aminocaproic acid (Amicar) and aprotinin (1 million KIU bolus + 0.25 million KIU/h infusion) [15]. The total amount of intraoperative estimated blood loss (EBL) was greater than 5 l (5,181 ml) in the placebo group, and only aprotinin was able to decrease EBL significantly (3,628 ml). The mean number of transfused pints was decreased with aprotinin (fresh-frozen plasma, from 9 to 0; platelets, from 3 to 0; RBC units, from 6 to 4). Once again, the efficacy of aprotinin was demonstrated in patients with major bleeding and large amounts of transfusion. Aprotinin also preserved the thromboelastogram mean clot-formation time, clot strength, and clotting index as compared with EACA or control.

A very small double-blinded study by Jeserschek included 18 patients scheduled for major orthopedic surgery (revision arthroplasty of the hip or knee ($n=16$), or for resection of a soft-tissue sarcoma ($n=2$)) [15]. Mean intraoperative blood loss was reduced from 1,957 ml in the control group to 736 ml in the aprotinin group (1 million KIU + 0.5 million KIU/h), and the mean requirement for intraoperative homologous blood transfusion in the aprotinin group was reduced to 1.4 units (95% confidence interval, 0;2–2.7) as compared with 3.1 units (1.7–4.6) in the control group. A non-significant decrease in the length of hospital stay was also observed.

Capdevila et al. demonstrated that aprotinin was able to dramatically reduce blood loss (1,783 ml vs 5,305 ml in the placebo group) and the number of packed RBC units (3 vs 7) used in patients undergoing major orthopedic surgery of the hip or pelvis for sepsis or malignant tumors [3]. Of note, preoperative donation and/or intraoperative cell-saving procedures are generally not performed in these cancer and/or septic patients, although massive intraoperative bleeding frequently occurs. These conditions and the severity of the patient's clinical condition, i.e., severe sepsis or cancer, provide a good rationale for the use of this type of hemostatic agent. The greater the bleeding the more beneficial the effects of aprotinin appears to be.

However, when the Capdevila study was published, the optimal aprotinin dose was still debated, and objective assessment of deep vein thrombosis was not systematically performed in these high-risk patients. Therefore, we decided to conduct a prospective, multicenter double-blinded dose-ranging study to compare the risk/benefit ratio of high- and low-dose aprotinin with placebo after major orthopedic surgery [28]. After IRB approval and informed consent, 58 patients were randomized into three groups:

- High-dose aprotinin, 4 million KIU bolus before surgery, followed by a continuous infusion of 1 million KIU/h until the end of surgery
- Low dose aprotinin, 2 million KIU bolus + 0.5 million KIU/h
- Placebo

Bleeding was measured and calculated. A bilateral ascending venography was systematically performed on the third postoperative day. Measured and calculated bleeding decreased in the high-dose-protinin group. (Calculated bleeding, whole blood, hematocrit (HT) 30%: 2,023 ml, range 633–4,113 ml; as compared with placebo, 3,577 ml, range 1,670–21,758 ml). The total number of homologous and autologous units also decreased significantly in the high-dose aprotinin group (2 units, range 0–5) as compared with placebo (4 units, range 0–42). No increases in clinical or venographic deep vein thrombosis or in pulmonary embolism were observed in the aprotinin-treated groups as compared with placebo. High-dose aprotinin was safe and effective in dramatically reducing the measured and calculated bleeding, and the amount of transfused RBC units. (Tables 1 and 2) One non-fatal allergic reaction was observed in one aprotinin-treated patient.

The results of the HACOL study show that, in patients undergoing major orthopedic surgery, high-dose aprotinin significantly reduced intraoperative and postoperative blood loss and packed RBC requirements. The observed difference between calculated bleeding and measured bleeding

Table 1 Bleeding in the HACOL study (HT hematocrit). Results are expressed as median and range

	Placebo (n=18)	Medium-dose aprotinin (n=22)	High-dose aprotinin (n=18)
Aspiration ± cell-saver (ml)			
Median	1,265	838	600
Range	(250–6,000)	(200–16,000)	(200–2,200)
Swabs (ml)			
Median	700	310	275
Range	(100–3,960)	(100–3,000)	(0–1,800)
Postoperative drainages (ml)			
Median	1,190	590*	625*
Range	(0–3,060)	(130–3,080)	(42–2,470)
Total measured bleeding (ml of whole blood)			
Median	2,795	1,943	1,715*
Range	(950–12,760)	(780–19,000)	(472–3,490)
Total calculated bleeding (ml of RBC units, HT 100%)			
Median	1,073	711	607*
Range	(501–6,528)	(315–3,900)	(190–1,234)
Total calculated bleeding (ml of whole blood, HT 30%)			
Median	3,577	2,370	2,023*
Range	(1670–21,758)	(1050–12,999)	(633–4,113)

* $p < 0.05$ vs placebo

Table 2 Transfusion in the HACOL study (RBC U red blood cell units; FFP fresh-frozen plasma units). Results are expressed as median, range and total amount of units per treatment group

	Placebo (n=18)	Medium-dose aprotinin (n=22)	High-dose aprotinin (n=18)
Homologous RBC U			
Median	2	0	0*
Range	(0–42)	(0–26)	(0–2)
Total	101	53	7
Number of exposed patients	11	8	4*
Homologous + autologous RBC U			
Median	4	3	2*
Range	(0–42)	(0–26)	(0–5)
Total	123	83	42*
Number of exposed patients	17	19	14
Cell-saver units			
Median	1	2	1
Range	(1–3)	(1–4)	(0–2)
Total	9	15	10
Homologous FFP units			
Median	0	0	0
Range	(0–13)	(0–12)	(0–2)
Total	13	12	2

* $p < 0.05$ vs placebo

provides additional data suggesting that occult postoperative bleeding (mainly hematomas) was also decreased by aprotinin.

Most of our patients fulfilled the inclusion criteria regarding perioperative bleeding, with median measured bleeding of 2,795 ml (900–12,760 ml), suggesting that, in patients scheduled for major orthopedic surgery, bleeding and transfusion are frequent and that blood-sparing protocols should systematically be part of the perioperative care of the patient. All our patients underwent spine, pelvic or hip surgery. Most of these procedures belong to one of the four supposed high-risk categories with regard to bleeding: revision, trauma, cancer and sepsis. The remaining patients were only operated on for the spine or pelvis. We initially thought that their theoretical bleeding risk would decrease slightly, as compared with the four other groups. Among all the patients of the study who bled more than 1,000 ml (calculated bleeding, HT 100%, $n=17/57$), 7/18 patients belonged in the “other-types-of-surgery” group (NS). Obviously, these procedures posed the same bleeding risk.

As a potent hemostatic agent and an in vitro inhibitor of activated protein C [9], aprotinin has been accused of inducing a hypercoagulable state and promoting graft occlusion after coronary artery bypass [1, 4] or liver transplantation [10]. It could theoretically increase the venous thromboembolic risk in patients undergoing major orthopedic procedures, despite the use of a daily low-molecu-

lar-weight prophylaxis. In studies of low-molecular-weight heparins (LMWH) in patients undergoing THR, the global venographic DVT rate on day 10 generally reached 15–25% in patients treated with LMWH [11]. The theoretical venographic DVT rate in our patients was supposed to be as high. Ours was the first double-blinded aprotinin study to assess, systematically, venous thromboembolism with a venography performed at day 3. The number of thromboembolic events was very low and not significantly different from one group to another. This is consistent with previous reports. However, in this regard, the sample of 58 patients is far too small to draw any definite conclusion or to rule out any prothrombotic effect of aprotinin. One can only notice that no thrombotic event was detected in the high-dose group and that, in our study, the increase in the aprotinin dose did not increase the thrombotic risk.

One non-fatal allergic reaction was recorded, leading to discontinuation of the treatment in a young patient. Since aprotinin is a polypeptide derived from bovine lungs, it possesses antigenic properties. Therefore, the possibility of an adverse reaction to this agent exists, especially in patients re-exposed to this drug. Allergic reactions after re-exposure have been described [5, 6]. The incidence of hypersensitivity reactions in one study was 2.8% in 248 patients re-exposed to aprotinin [7]. A time dependency for the risk of adverse reactions exists: the shorter the time interval between the two exposures, the higher the risk of a reaction. Therefore, the drug should not be given within 6 months after the last exposure. In addition, exposure of patients with moderate expected bleeding (i.e., patients scheduled for total hip replacement) to this significant allergic risk does not seem to be justified, considering the potential severity of aprotinin-induced anaphylactic shock.

Two doses of aprotinin were compared with placebo in the HACOL study: the low dose, as already described in several papers, and a higher dose. Our original hypothesis was based on an equal efficacy of the two doses. However, the final results showed a clear benefit for the high

dose over the placebo. The results in the low-dose group did not reach statistical significance, despite a real efficacy. In the high-dose group, however, bleeding and the total amount of blood transfusion decreased dramatically. It could be assumed that intraoperative bleeding is responsible for a partial washout of the product. Low doses could be beneficial in cardiac surgery when shed blood is immediately reinfused in the bypass, but appear ineffective when a consistent blood volume is discarded. A high plasma concentration has to be reached [21], and a continuous infusion of a high dose seems to be mandatory to maintain such a level. Furthermore, higher doses may be responsible for a larger decrease in thrombin generation than common doses. An indirect anticoagulant effect of high-dose aprotinin could be reported, in conflict with the supposed prothrombotic effect of high doses.

Our results clearly demonstrate that prophylactic high-dose aprotinin was able to dramatically decrease perioperative blood loss, RBC transfusion and the number of patients exposed to transfusion in major orthopedic surgery, without any significant side-effects. In high-risk orthopedic patients who haven't already been exposed to the product, aprotinin use should be considered.

Conclusion

It is now well-recognized that major orthopedic surgery is associated with an increased risk for perioperative bleeding and subsequent need for blood transfusion [18, 24]. Therefore, aprotinin should be dedicated to this type of procedure. Mainly extensive spine surgery, cancer or sepsis surgery are concerned. However, as already observed, aprotinin has sometimes been effective in revision hip studies, since the total amount of bleeding was high. In addition, although data are scarce, aprotinin does not seem to increase the risk of deep vein thrombosis. The only major side-effect could be the potential occurrence of an anaphylactoid reaction. Finally, the decision should be guided by a risk/benefit analysis.

References

1. Alderman EL, Levy JH, Rich JB, Nili M, Vidne B, Schaff H, Uretzky G, Pettersson G, Thijs JJ, Hantler CB, Chaitman B, Nadel A (1998) Analyses of coronary graft patency after aprotinin use: results from the International Multicenter Aprotinin Graft Patency Experience (IMAGE) trial. *J Thorac Cardiovasc Surg* 116:716–730
2. Amar D, Grant FM, Zhang H, Boland PJ, Leung DH, Healey JA (2003) Antifibrinolytic therapy and perioperative blood loss in cancer patients undergoing major orthopedic surgery. *Anesthesiology* 98: 337–342
3. Capdevila X, Calvet Y, Biboulet P, Biron C, Rubenovitch J, D'Athis F (1998) Aprotinin decreases blood loss and homologous transfusions in patients undergoing major orthopedic surgery. *Anesthesiology* 88:50–57
4. Cosgrove D 3rd, Heric B, Lytle B, Taylor P, Novoa R, Golding L, Stewart L, McCarthy P, Loop FD (1992) Aprotinin therapy for reoperative myocardial revascularization: A placebo-controlled study. *Ann Thorac Surg* 54: 1031–1038
5. Dewachter P, Mouton C, Masson C, Gueant JL, Haberer JP (1993) Anaphylactic reaction to aprotinin during cardiac surgery [letter]. *Anaesthesia* 48: 1110–1111

6. Diefenbach C, Abel M, Limpers B, Lynch J, Ruskowski H, Jugert FK, Buzello W (1995) Fatal anaphylactic shock after aprotinin reexposure in cardiac surgery. *Anesth Analg* 80:830–831
7. Dietrich W (1998) Incidence of hypersensitivity reactions. *Ann Thorac Surg* 65 [Suppl]:S60–S74
8. Engel JM, Hohaas T, Ruwoldt R, Menges T, Jurgensen I, Hempelmann G (2001) Regional hemostatic status and blood requirements after total knee arthroplasty with and without tranexamic acid or aprotinin. *Anesth Analg* 92:775–780
9. Espana F, Estelles A, Griffin J, Aznar J, Gilabert J (1989) Aprotinin (Trasylo) is a competitive inhibitor of activated protein C. *Thromb Res* 56:751–756
10. Fitzsimons MG, Peterfreund RA, Raines DE (2001) Aprotinin administration and pulmonary thromboembolism during orthotopic liver transplantation: report of two cases. *Anesth Analg* 92:1418–1421
11. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr, Wheeler HB (2001) Prevention of venous thromboembolism. *Chest* 119: 132S–175S
12. Godet G, Bertrand M, Samama CM, Barré E, Fléron MH, Baron JF, Coriat P, Kieffer E, Viars P (1994) Aprotinin decreases blood loss and blood transfusion requirements in thoracic and thoraco-abdominal aortic surgery under extra-corporeal circulation. *Ann Vasc Surg* 8:452–456
13. Hayes A, Murphy DB, McCarroll M (1996) The efficacy of single-dose aprotinin 2 million KIU in reducing blood loss and its impact on the incidence of deep venous thrombosis in patients undergoing total hip replacement surgery. *J Clin Anesth* 8:357–360
14. Janssens M, Joris J, David JL, Lemaire R, Lamy M (1994) High-dose aprotinin reduces blood loss in patients undergoing total hip replacement surgery. *Anesthesiology* 80:23–29
15. Jeserscheck R, Clar H, Aigner C, Rehak P, Primus B, Windhager R (2003) Reduction of blood loss using high-dose aprotinin in major orthopaedic surgery. A prospective, double blind, randomized and placebo-controlled study. *J Bone Joint Surg Br* 85B: 174–177
16. Kasper SM, Elsner F, Hilgers D, Grond S, Rutt J (1998) A retrospective study of the effects of small-dose aprotinin on blood loss and transfusion needs during total hip arthroplasty. *Eur J Anaesthesiol* 15:669–675
17. Khoshhal K, Mukhtar I, Clark P, Jarvis J, Letts M, Splinter W (2003) Efficacy of aprotinin in reducing blood loss in spinal fusion for idiopathic scoliosis. *J Pediatr Orthop* 23:661–664
18. Kovcsi T, Royston D (2003) Pharmacological approaches to reducing allogeneic blood exposure. *Vox Sang* 84: 2–10
19. Langdown AJ, Field J, Grote J, Himayat H (2000) Aprotinin (Trasylo) does not reduce bleeding in primary total hip arthroplasty. *J Arthroplasty* 15: 1009–1012
20. Lentschener C, Cottin P, Bouaziz H, Mercier FJ, Wolf M, Aljabi Y, Boyer-Neumann C, Benhamou D (1999) Reduction of blood loss and transfusion requirement by aprotinin in posterior lumbar spine fusion. *Anesth Analg* 89: 590–597
21. Levy JH, Bailey JM, Salmenpera M (1994) Pharmacokinetics of aprotinin in preoperative cardiac surgical patients. *Anesthesiology* 80:1013–1018
22. Murkin JM, Shannon NA, Bourne RB, Rorabeck CH, Cruickshank M, Wyile G (1995) Aprotinin decreases blood loss in patients undergoing revision or bilateral total hip arthroplasty. *Anesth Analg* 80:343–348
23. Murkin JM, Haig GM, Beer KJ, Cicutti N, McCutchen J, Comunale ME, Hall R, Ruzicka BB (2000) Aprotinin decreases exposure to allogeneic blood during primary unilateral total hip replacement. *J Bone Joint Surg Am* 82: 675–684
24. Porte RJ, Leebeek FWG (2002) Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. *Drugs* 62:2193–2211
25. Porte RJ, Molenaar IQ, Begliomini B, Groenland TH, Januszkiewicz A, Lindgren L, Palareti G, Hermans J, Terpstra OT, for the EMSALT Study Group (2000) Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomised double-blind study. *Lancet* 355: 1303–1309
26. Royston D, Bistrup BP, Taylor KM, Sapsford RN (1987) Effects of aprotinin on need for blood transfusion after repeat open-heart surgery. *Lancet* 2:1289–1291
27. Samama CM, Dietrich W, Horrow J, Taby O, Samama MM (2000) Structure, pharmacology, and clinical use of antifibrinolytic agents. In: Bachman F (ed) *Handbook of experimental pharmacology. fibrinolytics and antifibrinolytics*. Springer, Berlin Heidelberg New York, pp 559–585
28. Samama CM, Langeron O, Rosencher N, Capdevila N, Rouche P, Pegoix M, Bernière J, Coriat P, for the HACOL Study Group (2002) Aprotinin versus placebo in major orthopedic surgery: a randomized double-blinded dose-ranging study. *Anesth Analg* 95:287–293
29. Thorpe CM, Murphy WG, Logan M (1994) Use of aprotinin in knee-replacement surgery. *Br J Anaesth* 73: 408–410
30. Urban MK, Beckman J, Gordon M, Urquhart B, Boachie-Adjei O (2001) The efficacy of antifibrinolytics in the reduction of blood loss during complex adult reconstructive surgery. *Spine* 26: 1152–1157